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Effort Angina With Adequate Beta-Receptor Blockade: Comparison With Diltiazem Alone and in Combination

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Calcium channel blockers and beta-receptor blockers improve symptoms of myocardial ischemia by potentially different mechanisms. Accordingly, combination therapy may entail additive benefits. Twenty-four patients with symptomatic stable effort angina despite full beta-blockade were randomized to a double-blind Latin square protocol in which they received propranolol in a dose producing full beta-receptor blockade, diltiazem, 240 mg/day, in divided doses and a combination of propranolol and diltiazem, 240 or 360 mg/day. Treadmill testing (Bruce protocol) was utilized to assess exercise tolerance, radionuclide ventriculography to assess left ventricular function and clinical follow-up to assess adverse effects and overall clinical response.

Comparable treadmill exercise times were observed with monotherapy (344 ± 83 seconds with propranolol and 341 ± 87 seconds with diltiazem) and the lower dose combination (361 ± 87 seconds). With propranolol and diltiazem, 360 mg/day, however, there was a significant increase in treadmill time (393 ± 106 seconds; $p < 0.05$). In five patients whose treadmill exercise was limited by angina on all therapies, there was a significant improvement in the time to onset of chest pain with both low dose and high dose combinations (311 ± 71 seconds, $p < 0.05$ and 336 ± 76 seconds, $p < 0.01$, respectively). Improved treadmill performance was supported by the clinical response, while an increase in adverse effects was not observed. Thirteen of 24 patients blindly selected the higher dose diltiazem combination as their optimal therapy.

Left ventricular dilation was observed (by radionuclide ventriculography) in response to exercise in each phase of therapy; this was related to stress-induced ischemia. Cardiac index was higher at rest (3.2 ± 0.6 liters/min per m^2) and during exercise (5.5 ± 1.2 liters/min per m^2) with diltiazem therapy in relation to an increased heart rate (rest 66 ± 8 beats/min, exercise 95 ± 10).

Combination therapy of propranolol and diltiazem (particularly with the higher diltiazem dose of 360 mg/day) results in significant improvement in exercise capacity and reduction in symptoms without an increase in adverse effects or significant deterioration of left ventricular function in patients who have continued symptoms of angina on monotherapy alone.

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Continuing and limiting angina of effort despite adequate beta-receptor blockade is a common clinical problem. The calcium channel blocking agents are a new class of therapeutic alternatives. Diltiazem, a relatively new member of this class, has been shown to prevent anginal symptoms and improve exercise tolerance in patients with coronary artery disease (1,2). This antianginal effect is thought to be related to an increase in coronary and subendocardial blood flow (3,4). Thus, calcium channel blockers appear to alleviate angina by different mechanisms from those of beta-blockers (5). Consequently, the potential for additional anginal relief with improved exercise tolerance might be possible with combination therapy.

In this study, the clinical efficacy of diltiazem alone and in combination with propranolol was evaluated in a group of patients who continued to be limited by exertional angina despite beta-blockade. The purpose of the study was twofold: 1) to determine whether an alternative form of therapy or combination therapy would be indicated; and 2) if combination therapy is effective, to determine whether there is any dose-related increase in adverse effects or impairment of left ventricular function.

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Methods

Study patients. Patients with a history of stable exertional angina with treadmill stress tests limited by angina and associated with 1 mm or greater horizontal or downsloping ST segment depression in the presence of adequate beta-receptor blockade were candidates for entry to the study. Full beta-blockade was defined as a maximal heart rate of less than 120 beats/min during stress testing and a propranolol dosage of at least 160 mg/day in divided doses. Patients with unstable angina, heart failure, cardiac rhythm disturbances or myocardial infarction within the past 3 months were excluded. All cardiac medications except propranolol were withdrawn for at least 1 week before patients entered the study.

Twenty-four patients were entered in the study. During the course of investigation, one patient died from myocardial infarction and one was withdrawn because of an intercurrent gastrointestinal illness. These patients were replaced in the protocol by two others. The final study group consisted of 19 men and 5 women with a mean age of 57 years (range 37 to 71). Eight patients had previous myocardial infarction and 19 patients had coronary angiography that demonstrated single, double and triple vessel disease in 5, 7 and 7 patients, respectively. All patients gave informed consent for this study, which was approved by the Health Sciences Standing Committee on Human Research of The University of Western Ontario.

Study design. Patients were randomized blindly to a 6 × 4 Latin square with 2 week treatment regimens consisting of propranolol in a dose sufficient to provide full beta-blockade, diltiazem 240 mg/day in divided doses, propranolol plus diltiazem 240 mg/day and propranolol plus diltiazem 360 mg/day in divided doses. Identical placebo tablets for propranolol and diltiazem were utilized so that all treatment protocols appeared identical to both the patient and physician.

Exercise testing. Patients underwent graded treadmill exercise testing (Bruce protocol) before entry into the protocol and at the end of each treatment period. Heart rate, blood pressure and a 12 lead electrocardiogram were recorded at the end of each stage, with the onset of chest discomfort, at peak exercise and every 2 minutes for 6 minutes into the recovery period. The PR interval, heart rate and extent of ST segment depression were measured from the electrocardiogram.

Radionuclide ventriculography. In vitro labeling of the patient's red blood cells was performed using 25 mCi of technetium-99m pertechnetate. Two minute gated images utilizing 16 frames per cardiac cycle were acquired at rest and at supine cycle exercise consisting of 3 minute stages of 25 W increments. Left ventricular end-diastolic, end-systolic and background regions of interest were determined manually in duplicate for calculation of ejection fraction. A calibrated, nongeometric method of determining left ventricular end-diastolic and end-systolic volumes was utilized ($r = 0.985$, SEE 3 ml versus contrast left ventriculography) from which the stroke volume and cardiac output were derived (6).

Statistical analysis. Paired two-tailed t test and two-way analysis of variance were used to determine statistical significance at or in response to exercise where appropriate.

Table 1. Adverse Effects in 24 Patients

	P	D	PD-1	PD-2
Fatigue	8	4	8	7
Dyspnea	2	2	4	2
Cold limbs	2			1
Sleep disturbance	2	2		
Edema		1		2
Headache	1	4	1	
Depression	1	3		1
Gastrointestinal upset		2	1	2

D = diltiazem, 240 mg/day; P = propranolol, mean dose 170 mg/day; PD-1 = propranolol plus diltiazem, 240 mg/day; PD-2 = propranolol plus diltiazem, 360 mg/day.

Table 2. Clinical Response to Therapy in 24 Patients

	P	D	PD-1	PD-2
Frequency of angina (no./week)	7 5 ± 7.2	10 0 ± 1 4	5.1 ± 7.4*‡	3 8 ± 4 4†‡
Nitroglycerin use (no./week)	7.9 ± 5.8	6.8 ± 12.5	4.3 ± 1 0§	2 5 ± 4.6§
Patient preference	3	3	5	13

*$p < 0.05$ versus propranolol; †$p < 0.01$ versus propranolol; ‡$p < 0.01$ versus diltiazem, §$p < 0.05$ versus diltiazem; values are mean ± SD. Abbreviations as in Table 1.

Results

Adverse effects (Table 1). In the course of study, reported adverse effects were relatively common; these were often mild, well tolerated and did not cause premature advancement from the treatment period or withdrawal from the trial. The feeling of fatigue was less frequent when patients were receiving diltiazem monotherapy than when they were treated with propranolol alone or in combination. Sensation of headache or depression appeared to be slightly more frequent in patients treated with diltiazem alone and was associated with a slight increase in frequency of angina of effort and nitroglycerin use.

Frequency of angina and nitroglycerin use (Table 2). Patients maintained a diary during each treatment period, recording each instance of angina and nitroglycerin

Table 3. Results of Treadmill Exercise Testing in 24 Patients

	P	D	PD-1	PD-2
Treadmill time (seconds)	344 ± 83	341 ± 87	361 ± 87	393 ± 106*†
Time to pain (seconds)	242 ± 55	278 ± 61	311 ± 71*	336 ± 77*†
Limitation by angina (no. pts.)	18	19	18	6
Limitation by fatigue (no. pts.)	6	5	6	18
Treadmill time (angina) (n = 5) (seconds)¶	307 ± 53	338 ± 76	347 ± 79	390 ± 71*†
Time to pain (n = 5) (seconds)¶	242 ± 55	278 ± 61	311 ± 71*	336 ± 76*‡
Heart rate (beats/min)				
Rest	58 ± 7‡	66 ± 6	54 ± 6‡	54 ± 8‡
Exercise	95 ± 10‡	113 ± 12	90 ± 11‡	89 ± 13*‡
Rate-pressure product (mm Hg/min)				
Rest	7,370 ± 1,220†	8,690 ± 1,480	6,770 ± 1,060†	6,540 ± 1,152†
Exercise	12,700 ± 2,730‡	17,080 ± 3,420	12,200 ± 2,340‡	11,790 ± 2,700*‡
ST segment depression (mm)				
Rest	−0.27 ± 0.36	−0.34 ± 0.45	−0.29 ± 0.36	−0.11 ± 0.31§‖
Exercise	−1.63 ± 0.97	−1.53 ± 0.84	−1.51 ± 0.72	−1.30 ± 0.78*†§
PR interval (ms)				
Rest	165 ± 27	158 ± 19*§	168 ± 23†	178 ± 21‡§
Exercise	161 ± 23	152 ± 17‖	158 ± 23	164 ± 26§

*$p < 0.05$ versus propranolol; †$p < 0.05$ versus diltiazem, ‡$p < 0.01$ versus diltiazem; §$p < 0.05$ versus PD-1, ‖$p < 0.01$ versus propranolol; ¶these were five patients who continued to be limited by angina during each treatment period. Values are mean ± SD. pts = patients; other abbreviations as in Table 1.

use for relief of chest discomfort. Low or high dose combination therapy was associated with fewer episodes of effort angina and less nitroglycerin use compared with either form of monotherapy. Frequency of chest pain and nitroglycerin use were slightly higher with diltiazem than with propranolol and with the low dose than with the high dose combination. There was no statistical difference between the two combinations or between the two monotherapies. Patients receiving either form of combination therapy, however, showed a significant improvement in anginal relief and nitroglycerin use compared with monotherapy. At the conclusion of the study and before the therapeutic codes were broken, the majority of patients (18 of 24) selected either the low dose (5 patients) or high dose (13 patients) propranolol plus diltiazem combination as the therapy of choice.

Treadmill exercise tests (Table 3). Total exercise duration and the time to onset of chest pain were similar for both forms of monotherapy and for low dose combination

Figure 1. Total treadmill time (**dotted bars**) is increased with less ST segment depression (**crosshatched bars**) with high dose combination therapy (PD-2) compared with propranolol (P) or diltiazem (D) monotherapy. Height of **bar** represents mean ± SD. D = diltiazem (240 mg/day); PD-1 = propranolol plus diltiazem (240 mg/day); PD-2 = propranolol plus diltiazem (360 mg/day); *$p < 0.05$ versus propranolol; +$p < 0.05$ versus diltiazem.

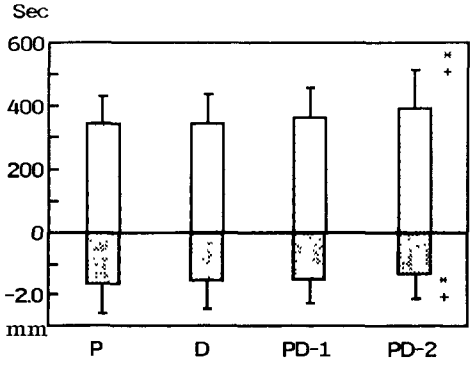
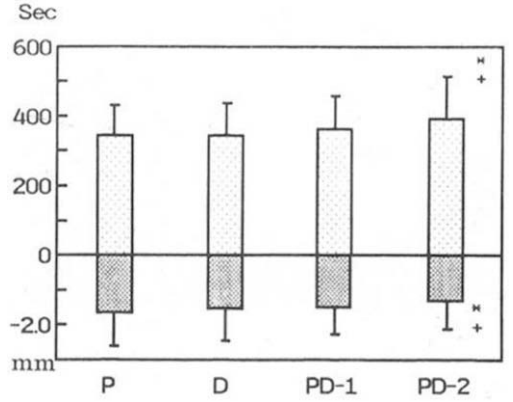


Figure 2. In the five patients whose treadmill exercise was limited by angina during each therapy, both treadmill time (**dotted bars**) and time to pain (**crosshatched bars**) were improved with the combination therapies compared with monotherapy alone. Additional improvement was attained with the higher dose combination. *$p < 0.05$ versus propranolol; +$p < 0.05$ versus diltiazem; + +$p < 0.01$ versus diltiazem; n = 5. Abbreviations as in Figure 1.



therapy. With the higher dose combination therapy, there was a significant increase in both treadmill time and time to onset of pain (Fig. 1). Only 5 of the 24 patients continued to be limited by angina during each treatment period. In this small subgroup, the pattern was slightly different. With monotherapy, treadmill times were comparable, whereas with each combination therapy there was further significant improvement in treadmill time and time to pain (Fig. 2).

Despite entry criteria that dictated that effort angina must be present in the face of adequate beta-blockade, 25% of the patients were no longer limited by angina, despite receiving identical therapy during the double-blind phase of the study. This decrease in exercise-induced angina was similar with diltiazem alone or with lower dose combination therapy. However, with the higher dose combination 75% of the patients stopped treadmill exercise because of fatigue and dyspnea rather than angina.

During exercise, the heart rate-systolic blood pressure (rate-pressure) product was significantly higher with diltiazem therapy. The rate-pressure product was similarly decreased with the lower combination therapy and propranolol therapy both at rest and at peak exercise. Further reduction in rate-pressure product during exercise occurred with the high dose combination therapy. This decrease was mediated largely by similar reductions in the heart rate response secondary to the beta-blockade.

Exercise was associated with comparable ST segment depression at peak stress with both forms of monotherapy and with the lower dose combination. The extent of ST segment depression was less with the higher dose combination at peak exercise (Fig. 1).

Atrioventricular (AV) conduction, as reflected by the PR interval, was significantly prolonged with the higher dose combination therapy. The difference was not as marked with exercise. No episodes of second or third degree heart block were observed.

Radionuclide ventriculography (Table 4, Fig. 3). Patients admitted to the study had no clinical evidence or history of heart failure in the face of full beta-blockade. By design, then, all patients had normal or near normal left ventricular function at rest.

At rest, left ventricular ejection fraction was slightly higher with both combination treatments compared with either form of monotherapy. Although left ventricular volumes—both end-systolic (Fig. 3c) and end-diastolic (Fig. 3a)—were similar with all treatments, the end-diastolic volume tended to be slightly smaller during diltiazem therapy. Consequently, the derived stroke volume calculation was similar with diltiazem monotherapy (Fig. 3b). Cardiac index, on the other hand, was significantly higher during diltiazem therapy secondary to a higher heart rate at rest (Fig. 3d).

With exercise, the left ventricular end-diastolic and end-systolic volumes (Fig. 3a,c) increased in a similar manner during each treatment type. Stroke volume also increased with all treatment modalities but to a slightly greater extent with combination therapy than with propranolol alone (Fig. 3b). As a result of the volume changes, ejection fraction was slightly higher at exercise with diltiazem and both combinations than with propranolol. Finally, as a result of the higher exercise heart rate with diltiazem therapy, cardiac index was higher than with other treatment modalities, which were similar to each other.

Table 4. Results of Radionuclide Ventriculography in 24 Patients

	P	D	PD-1	PD-2
EDVI (ml/m^2)				
Rest	102 ± 27	96 ± 27	100 ± 22	102 ± 27
Exercise	111 ± 29‖	111 ± 33‖	114 ± 31‖	115 ± 31
ESVI (ml/m^2)				
Rest	46 ± 18	43 ± 16	43 ± 15	43 ± 16
Exercise	51 ± 20‖	49 ± 23§	48 ± 18‖	50 ± 20‖
SVI (ml/m^2)				
Rest	56 ± 11	53 ± 13	57 ± 11†	57 ± 13†
Exercise	60 ± 12§	62 ± 14‖	66 ± 18*‖	66 ± 17*‖
Heart rate (beats/min)				
Rest	59 ± 11‡	66 ± 8	55 ± 7*‡	54 ± 8*‡
Exercise	83 ± 11‡	95 ± 10	79 ± 9‡	80 ± 13*‡
Ejection fraction (%)				
Rest	57 ± 9	57 ± 7	59 ± 7*†	59 ± 7*†
Exercise	56 ± 9	58 ± 10*	59 ± 8*	58 ± 9*
Cardiac index (liters/min per m^2)				
Rest	3.0 ± 0.6†	3.2 ± 0.6	2.9 ± 0.6†	3.0 ± 0.6†
Exercise	4.6 ± 0.8‡	5.5 ± 1.2	4.9 ± 1.4†	5.0 ± 1.8†

*p < 0 05 versus propranolol; †p < 0.05 versus diltiazem; ‡p < 0.01 versus diltiazem; §p < 0.05 versus rest; ‖p < 0.01 versus rest. Values are mean ± SD. EDVI = end-diastolic volume index; ESVI = end-systolic volume index; SVI = stroke volume index, other abbreviations as in Table 1.

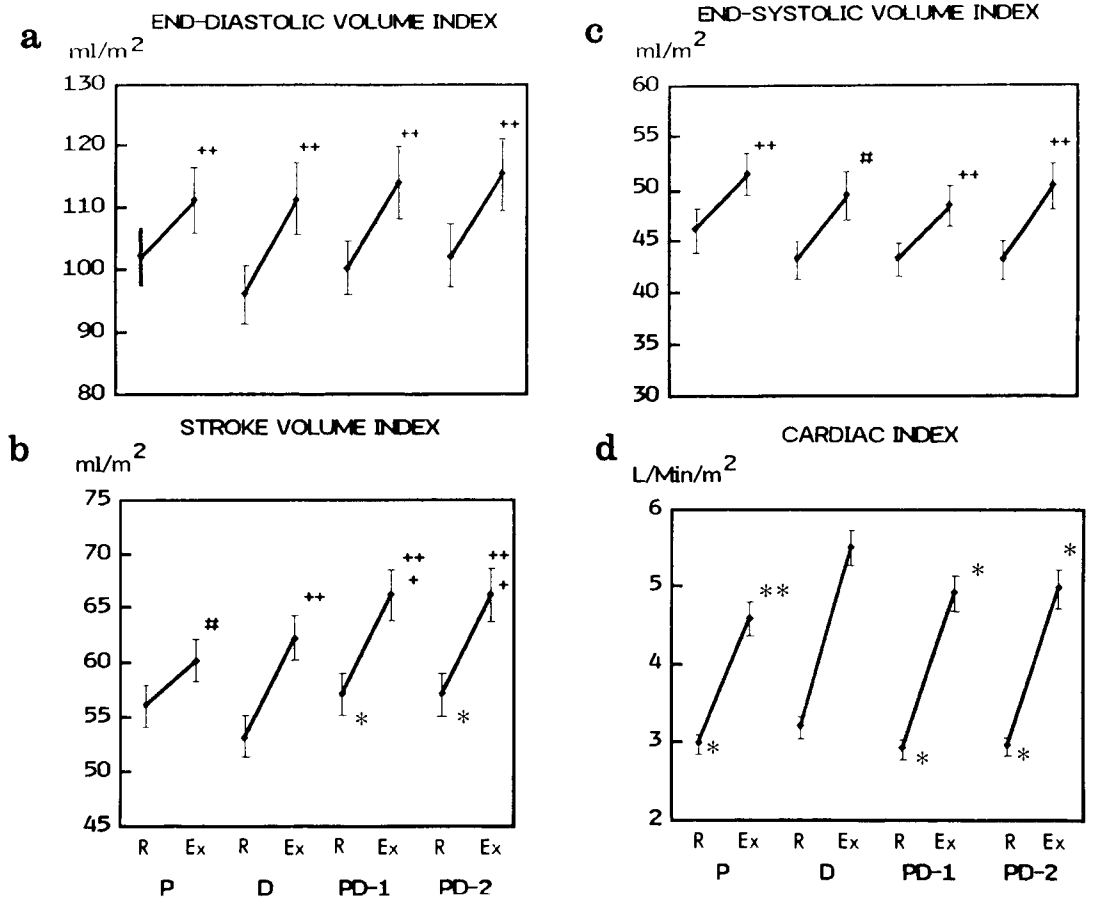


Figure 3. The left ventricular volume response for each therapy is shown both at rest (R) and during exercise (Ex). End-diastolic volume (**a**) and end-systolic volume (**c**) increased with exercise as a manifestation of stress-induced left ventricular dysfunction secondary to ischemia. Stroke volume (**b**) improved with exercise to a greater extent with combination therapy compared with propranolol. Cardiac index (**d**) was higher at rest and exercise with diltiazem, secondary to a higher heart rate. *p < 0.05 versus diltiazem; +p < 0.05 versus propranolol; **p < 0.01 versus diltiazem; ++p < 0.01 versus rest; #p < 0.05 versus rest. Abbreviations as in Figure 1.

Discussion

Clinical efficacy. Previous studies have clearly demonstrated that as monotherapy, diltiazem is an effective antianginal agent at a dose of 240 mg/day (1) with some additional apparent improvement at 360 mg/day (7,8). Hung et al. (7) assessed exercise performance using combination propranolol and diltiazem therapy. Although, unlike our study, they did not demonstrate an increased exercise tolerance using combination therapy compared with single agent therapy, they did observe similar efficacy of the combination in suppressing exercise-induced symptoms of angina associated with a decrease in ST segment depression. In our study group, results of combination therapy with lower dose diltiazem were no different from those of either propranolol or diltiazem alone at the same dosage with regard to total treadmill time, anginal frequency, nitroglycerin use or adverse effect. With the higher dose diltiazem-propranolol combination, there was significant subjective and objective improvement in each of these variables without any increase in adverse effects. This was also reflected by the patients' own preferences for this therapy. Furthermore, in the subgroup of five patients who continued to be limited by angina on the treadmill, the superiority of the higher dose combination was maintained. Again, this improvement occurred without any increase in adverse effects.

Individual variability. Although the entry criteria for this study necessitated that patients have angina during treadmill exercise while receiving beta-blocker therapy, 25% of patients during the double-blind phase were limited only by fatigue on treadmill testing while receiving identical therapy (propranolol). In addition to placebo effect, this finding reflects the individual variability of patients with angina as recently addressed by Starling et al. (9). They observed a large variability in treadmill times with sequential testing, although the rate-pressure product remained relatively consistent at peak exercise. Starling et al. also observed a 10% spontaneous remission of exercise-induced angina during the course of a single day. This individual variability appears to account for some remission in effort angina. Neverthe-

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less, despite these individual variabilities, the group means for treadmill time remain consistent (9,10).

Myocardial performance. Although no patient with serious left ventricular dysfunction was included in this study, and although monotherapy with diltiazem and propranolol has only minor negative inotropic effects, potential deterioration of left ventricular function with the combination is of concern. In our study, the alteration in left ventricular function observed during rest and exercise was similar irrespective of the therapeutic regimen. During supine exercise, there was dilation of the heart with an increase in both end-diastolic and end-systolic volumes. Consequently, there was a slight but statistically significant increase in ejection fraction both at rest and during exercise with each combination therapy. While this increase is of no clinical significance, the important physiologic interpretation of this observation is the lack of deterioration in left ventricular function with combination therapy, although this may not apply to patients with serious left ventricular dysfunction. The alterations observed in stroke volume and cardiac index are a reflection of the summation of effects on end-diastolic volume and heart rate. With diltiazem alone, the rest and peak exercise heart rates are higher than those seen with propranolol alone or combination therapy. Consequently, the diastolic filling period would be reduced, leading to a small decrease in end-diastolic volume and stroke volume. This difference in heart rate is associated with a significantly higher cardiac index with diltiazem therapy.

Mechanism of angina reduction. A different mechanism of action for propranolol and diltiazem is reflected by the significantly different heart rate and rate-pressure product in the setting of comparable treadmill times and extent of ST segment depression. With combination therapy, however, the anti-ischemic action appears to be dependent mainly on the rate-pressure product, suggesting counterbalancing effects from each drug. It would appear that the lower dose combination therapy provides little advantage over monotherapy. One might speculate that beta-blocker therapy interferes with improvement in collateral and subendocardial blood flow afforded by the addition of the lower dose of diltiazem. This effect may be partially overcome by a higher dose of diltiazem resulting in improvement in anginal prophylaxis which is associated with improvement in treadmill exercise duration and reduction in ST segment depression at peak exercise despite a similar rate-pressure product. The magnitude of the interaction appears heavily weighted in the direction of the effects of beta-blockade. Even with the higher dose diltiazem combination, the extent of ST segment depression is more closely associated with an altered rate-pressure product, similar to that seen with propranolol alone or in combination with diltiazem given at the lower dose. Hung et al. (7) made similar observations and showed that diltiazem given at 360 mg/day in divided doses was comparable with a similar combination of propranolol and diltiazem for the relief of angina and improvement in exercise tolerance.

When the therapeutic intervention suppresses the target symptoms, problems arise with group analysis. In the study of Hung et al. (7), 12 patients had effort angina, of whom 11 had associated diagnostic ST segment shift. With propranolol therapy alone these investigators were left with only eight patients with exercise-induced angina with a further reduction to six with diltiazem alone or combination therapy. Thus, group analysis includes a significant proportion of patients who were now angina-free and may be limited in their exercise performance by symptoms unrelated to their heart disease. Further, the failure to demonstrate a difference in a small group of patients may reflect a type II statistical error. The same difficulties arise in analysis of our entire patient group. However, when only the patients who were limited by exercise angina with each therapeutic intervention are considered, there is clear benefit with each combination therapy over monotherapy with respect to both total treadmill time and time to onset of pain (Fig. 2).

Conclusions. Anginal symptoms may regress spontaneously during the course of 1 month in a significant number of patients if therapy is left unchanged. In patients who continue to be limited by angina despite adequate beta-blockade, further alleviation of symptoms and increase in exercise capacity may be observed with the addition of diltiazem. A higher dose of diltiazem (360 mg/day) is more effective in combination with propranolol than a lower dose (240 mg/day) for anginal prophylaxis. Of considerable importance is the lack of any deleterious effect on left ventricular function or of increased adverse clinical effects with such combination therapy. Moreover, in patients who experience adverse effects of fatigue, lassitude or troublesome dreams while receiving propranolol therapy alone, diltiazem as a single agent therapy can provide identical anginal prophylaxis without the adverse effects.

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